REMARKS

Claims 6, 7, 27, and 33 – 35 are pending. Claim 35 has been amended to correct a typographical mistake.

Claim Rejections – 35 U.S.C. § 112, first paragraph

Claims 6, 7, 27, and 33 – 35 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Applicants respectfully traverse.

The Examiner contends that the phrase "wherein detecting modification comprises the additional step of quantifying the amount of the inactive MEK or inactive MAPK proteins..." is not supported in the as-filed specification. Office Action, page 3. Support of the amendment can be found in Example 3 (including paragraphs [0135]-[0136] and Figure 3). Example 3 discloses inactive MEK/MAPK and the kind of modification made to them (phosphorylatation). Thus, claims 6, 7, 27, and 33 – 35 are supported by the specification as originally filed and Applicants request withdrawal of this rejection.

The Examiner also contends that the specification fails to provide an adequate written description of how an inactive MEK and MAPK immobilized on a polymer gel mask has been modified simply by exposing it to a solution of active Raf proteins and MEK and potential inhibitors of RAF or active MEK. Office Action, pages 3-4. Applicants point out that how an inactive MEK and MAPK can be modified by exposing it to active RAF and MEK proteins is disclosed in the specification.

Specifically, paragraph [0106] discloses an exemplary pathway that involves proteins A, B, and C. In this pathway, active A activates B and active C activates A. It further discloses an exemplary array in which inactive A and inactive B are immobilized, and are exposed to a solution containing active A, active C, and a potential inhibitor of the pathway. Paragraph [0124] further discloses that the present invention could be used to study biological pathways such as the MAPK cascades, an example of which is

Ras/Raf/MEK/ERK. Paragraph [0135] discloses that an array according to the present invention can be used to monitor the Raf/MEK/MAPK pathway, which is schematically illustrated in Figure 3. It is clear from the description in paragraphs [0106] and [0135] and the illustration in Figure 3 that Raf corresponds to C, MEK corresponds to A, and MAPK corresponds to B. Thus in this pathway, active Raf activate MEK, and active MEK activates MAPK. Inactive MEK and inactive MAPK are immobilized, and are exposed to a solution containing active MEK, active Raf, and potential inhibitor(s).

The Examiner further contends that it is not apparent from the claims what is being actually claimed i.e., modification of an inactive immobilized MAPK or MEK or the different potential inhibitors of the active Raf or MEK. Office Action, page 4. Applicants point out that the claims are directed to a method for detecting modification of MEK proteins or MAPK proteins of a Raf/MEK/MAPK pathway. The method can be used to study potential inhibitors of the active Raf or MEK. For example, since active Raf activates inactive MEK, an inhibitor of active Raf would inhibit the activation of inactive MEK. The lack of activation of inactive MEK can be detected by using the method claimed, thereby identifying the inhibitor of active Raf. Such a mechanism is described in paragraphs [0135]-[0136] and well-illustrated in Figure 3.

The Examiner states that it is not apparent from Example 3 and Figure 3 as to the different potential inhibitors of MEK or Raf as the disclosure simply describes broadly inhibitors and not a single specific inhibitor. Applicants respectfully point out that specific inhibitors does not have to be disclosed by the specification, because at least some potential inhibitors are well-known in the art, and because the present invention claims a method to screen a large variety of potential inhibitors to identify inhibitors of active Raf or MEK.

The Examiner further states that the specification does not describe the kind, type, location and other modifications made to the immobilized inactive MEK or MAPK. Applicants respectfully point out that specification does disclose a specific modification made to the immobilized inactive MEK or MAPK. Paragraph [0033] states that one biomolecule may modify the other, such that the modified biomolecule is, for example, activated or inactivated. In the particular case of Example 3, immobilized inactive MEK

is modified by active Raf, thereby activated; immobilized inactive MAPK is modified by active MEK, thereby activated. More specifically, the modification disclosed by Example 3 is phosphorylation. See paragraphs [0135]-[0136].

The Examiners asks whether the modification(s) result in the activation of the inactive MEK and MAPK, and if so whether the potential inhibitors have no effect on the now activated MEK and MAPK. The Examiner further asks what the differentiating features of the active or inactive MEK would be such that the inhibitor binds to one and not the other. As stated in the above paragraph, the modification in Example 3 results in the activation of the inactive MEK and MAPK. As disclosed in paragraph [0106], inactive A (in this case MEK) and inactive B (in this case MAPK) are immobilized and therefore cannot react with each other. Therefore, even though the inhibitor could have an effect on the newly-activated MEK, such effect would not show because the newly-activated MEK is still immobilized and does not react with the inactive MAPK.

For at least the reasons stated above, Applicants submit that claims 6, 7, 27, and 33 – 35 comply with the written description requirement. Withdrawal of the rejections is respectfully requested.

Claim Rejections – 35 U.S.C. § 112, second paragraph

Claims 6, 7, 27, and 33 – 35 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particular point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse.

Specifically, claim 35 is rejected under 35 U.S.C. § 112, second paragraph as allegedly being incomplete for omitting essential steps, such omission amounting to a gap between steps. The Examiner contends that the step by which the modification of the inactive MEK proteins or MAPK is detected is omitted. Applicants point out that the step of detecting modification of the inactive MEK or MAPK is claimed in step (e) of claim 35, and therefore is not omitted.

The Examiner contends that it is unclear as to the kind, extent and other modifications obtained by the claimed process on the inactive MAPK or MEK immobilized on a substrate. Applicants point out that claim 35 is directed to a method for

detecting modification of MEK proteins or MAPK proteins of a Raf/MEK/MAPK pathway. Claim 35 is not limited to any single kind of modification or detection method. However, Example 3 does disclose one example of the modification to be detected, namely phosphorylation. The specific method for detecting phosphorylation is also disclosed. Paragraph [0135] describes that antibodies that are specific to phosphorylated resides of MEK and MAPK are incubated on the array. Only those immobilized proteins that have been phosphorylated, and thus bound to the antibodies, would be detected. Those immobilized proteins that have not been phosphorylated due to the inhibitors acting on the corresponding active Raf or MEK would not bind to the antibodies, and therefore would not be detected because unbound antibodies are washed away.

The Examiner's contention that the claim and Example 3 contain the same process steps, yet determine effect(s) is also misplaced. As stated above, claim 35 is directed to the method of detecting modification in general. Example 3 discloses an example of modification and the detection method of that modification. Using the method, inhibitors of Raf or MEK can be identified. The claim is not inconsistent with Example 3.

The Examiner alleges that claim 34 is unclear as to how the inactive MEK and MAPK proteins self-assembled into a monolayer. Office Action, page 5. Applicants submit that while the method claimed in claim 34 does require the forming of a self-assembled monolayer (SAM), it does not require the inactive MEK or MAPK proteins to self-assembled into a monolayer. Instead, inactive MEK or MAPK proteins bind to the SAM. The specification discloses SAM in at least paragraphs [0029], [0052], and [0077]-[0091].

For at least the reasons stated above, Applicants submit that claims 6, 7, 27, and 33–35 are not indefinite. Withdrawal of the rejections is requested.

Claim Rejections – 35 U.S.C. § 103, over Duesbery

Claims 6, 7, 27, and 33 – 35 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Duesbery (US 6,485,925). Applicants respectfully traverse because a *prima facie* case of obviousness has not been established.

To establish a *prima facie* case of obviousness, *inter alia*, the prior art reference must teach or suggest all the claim limitations. M.P.E.P. §2143. Here, many of the limitations of independent claim 35 are not taught or suggested by Duesbery.

The Examiner states that Duesbery does not specifically disclose an immobilization of inactive MEK or MAPK on a substrate of the polymer gel contact mask, but alleges that the immobilization would have been obvious to one of ordinary skill in the art. Office Action, page 9.

First, Applicants point out that independent claim 35 does not recite a "substrate of polymer gel contact mask." Step (a) of claim 35 recites "placing a polymer gel contact mask having holes on a substrate;" step (b) of claim 35 recites "immobilizing inactive MEK proteins and inactive MAPK proteins on areas of the substrate underlying the holes of the polymer gel contact mask." Therefore, the immobilization of the inactive MEK and MAPK proteins is on the substrate, not on the polymer gel contact mask.

Second, Duesbery does not teach or suggest a polymer gel contact mask or the immobilization of inactive MEK and MAPK proteins on a substrate, as instantly claimed. The Matrigel disclosed by Duesbery is used to culture cells, not to mask a substrate onto which inactive MEK and MAPK proteins can bind. See col. 16, line 38-46. No immobilization of inactive MEK and MAPK proteins is disclosed.

Furthermore, other limitations of claim 34, such as exposing inactive MEK and MAPK proteins to a solution of active Raf and MEK proteins, ATP, and potential inhibitors and allowing binding of the active Raf and MEK proteins to the inactive MEK and MAPK proteins, are not taught or suggested by Duesbery either. Duesbery merely discloses exposing whole cells, cell extracts, or MAPK protein to anthrax lethal factor (LF), without specifying the activation status of the MAPK protein. See Examples I-III. There is not teaching or suggesting of inactive MEK and MAPK proteins, active Raf and MEK proteins, or the binding thereof.

For at least the reasons stated above, it would not have been obvious to one of ordinary skill in the art, in view of Duesbery, to come up with the present invention. Because a *prima facie* case of obviousness has not been established, Applicants submit

that claims 6, 7, 27, and 33–35 are patentable over Duesbery. Withdrawal of the rejections is requested.

Claim Rejections – 35 U.S.C. § 103, over Ruggieri in view of Mitsuhashi

Claims 6, 7, 27, and 33 – 35 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ruggieri (US 6,511,825) in view of Mitsuhashi (WO01/07164). Applicants respectfully traverse because a *prima facie* case of obviousness has not been established.

To establish a *prima facie* case of obviousness, *inter alia*, the prior art reference must teach or suggest all the claim limitations. M.P.E.P. §2143. Here, many of the limitations of independent claim 35 are not taught or suggested by the references.

The Examiner admits that Ruggieri does not teach immobilizing the kinase to a substrate with a polymer gel contact mask (gasket) in a multiwell plate, but states that Mitsuhashi discloses a gasket adapted for use with a multiwell microplate, and suggests that such a gasket is a polymer gel mask. Office Action, pages 13-14.

First, Applicants point out that the gasket disclosed in Mitsuhashi is not a polymer gel mask as instantly claimed. Mitsuhashi's gasket is not gel. Instead, it is made of hard material, as indicated by the list of preferred materials, and by the fact that the gasket sheet may have an edge adapted to be connected to a vacuum source. See page 1, lines 27 – 33.

Second, the references do not teach or suggest immobilizing inactive MEK and MAPK proteins on a substrate, as instantly claimed. The Examiner contends that it would have been obvious to one having ordinary skill in the art to use an array with a gasket in the method of Ruggieri, because the use of array is conventional in the art and is employed for high throughput screening of compounds. Office Action, pages 13-14. Applicants respectfully point out that there is no teaching or suggestion in Ruggieri that a high throughput screening of compounds is needed. Ruggieri discloses methods of identifying agents which modulate cellular transformation mediated by Ras and SRK, all

of which involve live cell growth assay. See col. 17, lines 10-64. There is no teaching or suggestion of using an array, let alone immobilizing inactive MEK and MAPK proteins on a substrate. Mitsuhashi discloses in general terms that gasket may be used, in combination with a multiwell filter plate, for, among other applications, biological and molecular biological assays. See page 5, lines 28 – 31. However, Mitsuhashi does not teach or suggest immobilizing any proteins, let alone immobilizing inactive MEK and MAPK proteins on a substrate.

Furthermore, other limitations of claim 34, such as exposing inactive MEK and MAPK proteins to a solution of active Raf and MEK proteins, ATP, and potential inhibitors and allowing binding of the active Raf and MEK proteins to the inactive MEK and MAPK proteins, are not taught or suggested by either of the references.

For at least the reasons stated above, it would not have been obvious to one of ordinary skill in the art, in view of Ruggieri and Mitsuhashi, to come up with the present invention. Because a *prima facie* case of obviousness has not been established, Applicants submit that claims 6, 7, 27, and 33–35 are patentable over Ruggieri and Mitsuhashi. Withdrawal of the rejections is requested.

CONCLUSION

It is respectfully submitted that the present application is now in condition for allowance, which action is respectfully requested. The Examiner is invited to contact Applicants' representative to discuss any issue that would expedite allowance of the subject application.

Any fees for extension(s) of time or additional fees required in connection with the filing of this response, are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is authorized to charge any such required fees or to credit any overpayment to Kenyon & Kenyon's Deposit Account No. 11-0600.

Respectfully submitted,
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Dated: August 7, 2006

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